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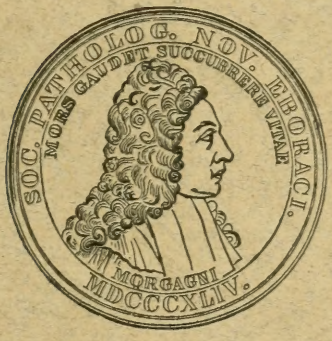
PROCEEDINGS

OF THE

NEW YORK PATHOLOGICAL SOCIETY



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DR. CHARLES NORRIS, *President.*

AN UNUSUAL CASE OF GENERALIZED TUMOR OF THE LYMPH NODES.

THOMAS FLOURNOY, M.D.

The autopsy on this subject and a large part of the subsequent work were done by Dr. Norris, to whom I am indebted for permission to present the case.

The clinical history is somewhat meager, the patient being a German who spoke and understood little English and was almost aphonic on account of certain throat conditions. He entered the service of Dr. Bryant of Bellevue Hospital, December 31, 1906. Dr. Bryant has very kindly given us permission to present the clinical history.

The patient was a male, forty-five years of age.

The family and previous personal history were negative. For fifteen years he had been employed in a grocery store. About two years ago, while in Harlem Hospital on account of a broken arm, there were removed from the right side of his neck several enlarged glands which he had first noticed about three months previously. Subsequent to this operation the remaining glands in the neck became enlarged, as did also the inguinal lymph nodes, though these latter in time again became small.

Three months after operation he became hoarse and had difficulty in swallowing. These symptoms increased gradually, but with periods of improvement.

About a year ago he entered City Hospital because of dyspnea. His legs at that time were swollen, and the glands in the neck were large and were considered inoperable. A tracheotomy was performed, evidently to relieve his dyspnea.

Little reliance can be placed on the clinical history for the reason that when his history was taken by another person he admitted that he had had enlarged glands in the neck for five years and said that he had been operated upon at the Presbyterian Hospital. Unfortunately there are no records of his admission either at the Harlem or Presbyterian Hospitals.

His chief complaint, when in the hospital, was weakness, dyspnea and swelling of the legs. There were present two scars, one from a curved surgical incision on the right side of the neck, and another in the median line as a result of the tracheotomy incision. Large, firm, nodular masses extended from the ear to the clavicle on the right side of the neck, and similar masses, smaller in size, were present on the opposite side of the neck. The right axilla was occupied by a large mass of nodes. In the opposite axilla, the nodes were smaller, but palpable. A

small subcutaneous nodule was present near the right nipple.

Enlarged glands were present in both Scarpa's triangles. Those on the right side were larger. The liver extended below the arch of the ribs, and the area of splenic dullness was large. The upper half of the abdomen was distended by an indefinite tumor mass. The left elbow was partially ankylosed, and the muscles of the upper and lower arms were atrophied from disuse. The left leg was edematous.

The urine was negative. Blood examinations revealed nothing noteworthy.

A provisional diagnosis of alveolar sarcoma was made from a specimen removed from the neck. The subcutaneous nodule near the right nipple was removed, and on examination the diagnosis of endothelioma was made by one of the leading pathologists in the City, Dr. Norris being at that time unwilling to express an opinion.

The patient died January 31, 1907. The post-mortem examination was made on February 2, 56 hours after death. Only the chief features of the examination need be given here:

The body was that of a large male, 6 ft. ¾ inches in height. On account of certain appearances suggesting acromegaly, more especially the form known as the *type carrée*, careful measurements were taken of the skull, face, hands, fingers and feet. In general, these indicated uniform enlargement of the fingers, especially of the right hand, and of both big toes. The significance of the enlargement of the right hand was, however, rendered difficult of interpretation on account of the existence of the old fracture of the left arm with atrophy of the muscles. The superior maxillary bones were enlarged and prominent. The lower jaw, nose and lips were normal in size.

The tongue, however, was large and broad, measuring from the epiglottis to the tip, 12 cm.; in breadth, 6.5 cm.; in thickness, 3 cm. The ears were symmetrical, very large and thick.

The abdomen contained several liters of clear fluid. A tumor mass weighing 1780 grams, was found in the upper median portion of the abdomen, displacing the stomach downward.

The left chest was filled with fluid, and the lung was collapsed. The right lung was voluminous, the bronchi containing mucopurulent exudate. Two of the bronchial lymph nodes were 4 to 5 cm. in length, and infiltrated with the tumor growth. The mediastinum was normal, with the exception of one small infiltrated lymph node. The thymus was absent.

The parietal pericardium was thickened and opaque, and showed small, raised nodules near the reflexion of the sac.

The heart was large, both ventricles hypertrophied. The mitral and aortic valves were slightly thickened. The aorta and vascular system presented no noteworthy lesion.

The liver weighed 1,580 grams. There was a moderate perihepatitis, with adhesions, and two small, firm whitish nodules about 3 to 4 mm. in diameter, were present beneath the capsule.

The spleen was small, fibrous, and firmly adherent to diaphragm, stomach and tumor mass. On its anterior border was an area of scar tissue which contained chalky material. Except for a large, left-sided varicocele, the genito-urinary tract was normal.

The kidneys were normal in size and appearance. The left suprarenal was large and firm, and contained a number of tumor nodules of varying size in the cortex

and medulla. The right suprarenal was normal. The tonsils were normal. The base of the tongue was somewhat glassy and smooth. The pharynx and larynx were normal.

Stomach: There was thickening of the muscular layers at the pyloric end of the stomach. About 2 inches from the pylorus, a large, teat-like process, with umbilication at the apex, was present. This was found to be composed of the greatly thickened muscular coats.

The small and large intestines were normal, except that on the posterior serous portions of the rectum there was a large whitish area, resembling inspissated purulent exudate.

All the cervical lymph nodes, especially on the right side of the neck, were greatly enlarged and infiltrated, forming packets which were adherent and continuous with the tumor mass occupying the right lobe of the thyroid gland.

The trachea and esophagus and the large vessels of the neck were practically embedded in the tumor mass and were compressed.

The left thyroid lobe was large but not involved. The right lobe, as referred to above, except for a few areas of normal thyroid tissue, was completely infiltrated.

The right axilla was almost completely occupied by large packets of lymph nodes, and several of the femoral lymph nodes on the right side were enlarged, the largest being about 3 cm. in length.

The tumor mass in the abdomen completely surrounded the pancreas, but the organ itself showed no involvement. The individual nodes were very large, firm, and adherent. The section was whitish and mottled with hemorrhagic foci.

The aorta and inferior vena cava, which passed

through the tumor mass, were greatly narrowed from compression.

The mesenteric nodes were small, yellowish in color, and not involved.

A striking picture was presented by the mesentery of the jejunum and upper ileum, upon which were situated a large number of small raised foci varying in size from a pin-point to the head of a small hat-pin. These nodules were yellowish-white in color.

The lacteals of the lower part of the small gut were injected and were the seat of small, whitish, dry and homogeneous foci.

The brain presented no gross lesions, except atheroma of the vessels and a small aneurysmal dilatation of the left vertebral artery. The sphenoid sinus contained thick, greenish-yellow purulent exudate. The middle ears were normal. The sella turcica and the pituitary gland were normal in size. On the inferior surface of the gland, a small, whitish nodule, 2 to 3 mm. in diameter, was present. This nodule was made up of tissue resembling in structure the neural lobe of the gland.

To recapitulate briefly, the case in its clinical aspects suggests a lymphosarcoma. Anatomically it likewise resembles a lymphosarcoma, the lymph nodes involved being the peripancreatic, cervical, axillary and femoral.

This diagnosis is, however, not borne out by the histological structure of the tumor which presents none of the characters of a lymphosarcoma or of a Hodgkin's or pseudoleukemia. No primary tumor was made out, although the involvement of the right lobe of the thyroid and the left suprarenal suggested such an origin. The posssibility of a primary focus of growth in one of these organs may be eliminated, first, by the histological structure, second, by the anatomical picture presented; namely,

generalized lymph node involvement of widely separated groups of nodes, without involvement of the viscera. (It may be stated here that the small nodules beneath the capsule of the liver were not neoplastic in origin.)

Two distinct histological pictures may be made out: The first was presented by all the infiltrated lymph nodes. The second was quite distinct from the first, and was presented alone by the thyroid gland.

The structure of the predominant type of tumor is distinctly alveolar and non-vascular. The septa vary in thickness, in some places being broad bands of fairly dense connective tissue, in other places being delicate connective tissue fibrillae with prominent nuclei. This latter appearance is especially well seen in the smaller alveoli.

The alveoli are in the main filled with closely packed cells having large, round or oval nuclei containing little chromatin. The protoplasm of the cells stains poorly, is homogeneous and abundant. The cell outlines are indistinct and in places appear to be directly continuous with the stroma, which is in places distinct.

Although this description applies to a large number of the lymph nodes examined, a few show marked differences which must be referred to. In places where the tumor is more actively growing, the growth tends to lose its alveolar character, although the connective tissue septa are broad and hyalin. The large alveoli in such nodes show a peculiar picture, the central portion being made up of apparently necrotic material, that is, of cells staining deeply with eosin and having pyknotic nuclei and chromatin dust.

The layer of tumor cells bordering this portion is compressed and fused, forming a narrow line of demarcation beyond which the tumor cells not only show no

evidence of compression but are unusually large and protoplasmic. The stroma about this type of nodule is extremely scanty and shows numerous small lymph spaces packed with tumor cells; in fact, the tumor seems to have every resemblance to an endothelioma.

The tumor nodules in the left adrenal show practically the same structure as do the tumors in the lymph nodes, the masses of cells being packed in alveolar spaces of various sizes. In this organ, however, there are masses which stain a bright red with eosin and with Van Gieson's stain exhibit a deep orange. With the other anilin dyes and in iodin solution, no amyloid reaction was obtained in celloidin sections. The character of this material is uncertain, although it presents striking similarities to amyloid, or to a hyalin substance with a peculiar staining reaction.

The tumor situated in, or replacing, the right lobe of the thyroid gland presents a different structure from that described above. This tumor is composed of closely packed groups of cells in alveoli of different sizes. The connective tissue framework is in places abundant; the stroma finely fibrillated and edematous, containing numerous fibroblasts. In many places it is infiltrated with small round cells. The outlines of the tumor cells are ill-defined; the nuclei of the cells are large and oblong in shape, and tend to arrange themselves in concentric striae, somewhat resembling epithelial pearls. The centers of the larger alveoli are occupied by an eosin-staining material, broken down cells, and chromatin dust. The thyroid tissue has been completely replaced.

The nodules on the mesentery of the jejunum and ileum are inflammatory in character.

The area on the rectal serosa consists of an exudate with large round or ovoid cells and a few plasma cells

and leucocytes. A few Gram-staining bacilli were found in the sections.

The case we have described is therefore a tumor involving the peripancreatic and retroperitoneal lumbar lymph nodes, and the left suprarenal. All the cervical nodes were greatly enlarged and infiltrated, and also the right sub-maxillary gland, the right lobe of the thyroid and the axillary lymph nodes on both sides. The lymph nodes in the chest, except for two large bronchial nodes and one mediastinal node, were not enlarged. Except for a few nodules on the diaphragm, the pleural surfaces and the lungs were free from involvement. This lack of involvement would seem to indicate that the two tumor masses were of separate origin.

Only in the thyroid does one find any evidence of the invasive power of the tumor, the lymph nodes, although adherent, being discrete and not tending to coalesce. No metastases were present in the liver, spleen, kidneys, heart, lungs or bones.

Although the tumor corresponds anatomically to the usual form of lymphosarcoma, this correspondence does not extend to the microscopic structure.

We believe that it is best to consider the tumor a primary lymph node endothelioma, which form of tumor has been described as arising from the reticulum and endothelium of the lymph spaces. The evidently multiple origin of the tumor is a feature which we wish to emphasize.

In a search of the literature, only one report of a similar case has been found. Gallina,* in 1903, described a tumor involving the cervical, retroperitoneal and mesenteric lymph nodes, and also both suprarenals. Gross section of parts of the tumor showed hyalin and

* *Virchow's Archiv*, Bd. 172.

cystic changes, and microscopic examination of all parts involved led to a diagnosis of endothelioma, arising from the lymph glands and lymph spaces.

A CASE OF BLASTOMYCOSIS.

GEORGE E. BREWER, M.D.

Dr. George E. Brewer presented a case of blastomycosis, giving the clinical history and the pathological report on the case made by Dr. F. C. Wood.

The patient was a young man, twenty-one years of age, of Russian birth, who had come to this country two years before. Eight months ago he had complained of pain between his shoulders which was increased on movement, and he was treated for muscular rheumatism. The pain, however, became worse, and he began to have a temperature. Two months ago he entered the Roosevelt Hospital for treatment. At that time he had a fluctuating swelling between the scapulae. A needle was introduced and a syringeful of dark colored pus was drawn out. It was thought that the condition was caries of the arch of the vertebra. An operation was performed, and on opening the abscess there was found a cavity which contained about six or seven ounces of dark colored pus, apparently mixed with blood. The spinous process of the third lumbar vertebra was distinctly involved. The second and fourth lumbar arches were also involved. The entire sac or wall of the abscess was dissected out, and the wound united by layer suture. The patient made a good recovery and the wound healed kindly. He remained perfectly well for about six or eight weeks

and then returned to the hospital with another fluctuating tumor over the first and second lumbar spines. This was larger than the first and there was considerable spinal rigidity. An incision was made and a large cavity was found filled with pus which was not mixed with blood. The abscess cavity seemed to be on the left side of the spine; one of the transverse processes was exposed and necrotic. The entire abscess cavity was again dissected out, and the patient did perfectly well for five or six days. There was apparently primary union in the wound. Two or three days later the wound was again dressed, after which the patient ran a temperature of 102° to 103° and the wound was re-opened. There was some retention of pus, and drainage was re-introduced. At the time of the report the patient had been normal for two or three days.

There had been practically no cough; a little sputum, however, was obtained by forced coughing, which showed nothing. There were no lesions of the skin and apparently no lesions in any other part of the body. The material was sent to the laboratory immediately after operation. Examination of the first syringeful of pus showed that the condition was one of blastomycosis. Afterwards the tissues were sent to the laboratory and cultures were made from them.

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The pus aspirated from the abscess cavity showed large numbers of spherical cells of different sizes, each surrounded by a clear gelatinous envelope. The fluid contained a large number of polynuclear and eosinophile cells, showing albuminous and fatty degeneration. These blastomycetes measured from 10 to 25 micra in

diameter. There was no evidence of budding in the organisms seen in the fresh pus. The wall of the abscess cavity was lined with granulation tissue and included a portion of the spine. The granulation tissue layer was about 1 cm. thick and was covered with a membrane of fibrin, leucocytes and red cells. In this membrane were embedded a considerable number of blastomycetes. The granulation tissue was very cellular, containing a moderate number of thin walled vessels and numerous polynuclear leucoytes. Scattered throughout the granulation tissue were many larger and smaller giant cells with nuclei ranged about the periphery of the cell and usually inclosing one or more blastomycetes. The inclosed organisms usually lacked a gelatinous envelope and also any internal structure. Frequently they were shrunken and evidently in process of destruction. The granulation tissue containing these organisms extended up between the muscle fibers of the spinal muscles and also invaded some of the fat tissue of the region. No organisms could be found in a small fragment of bone which was removed at the time of operation.

Cultures were made from the pus obtained from the first operation and an organism was isolated which grew easily though slowly on ordinary culture media. The formation of a mycelium in cultures was not observed.

Discussion.

Dr. James Ewing said that reports were steadily multiplying of cases of blastomycosis, or coccidioidal granuloma. The relation between these diseases was not yet clear, but most of them seemed to belong in the group of oidiomycosis. Of coccidioidal granuloma, Brown, in the *Journal of the American Medical Associ-*

ation, had recently collected nineteen cases; but he did not make it clear that all of them differed from oidiomycosis. The latter infection was more common, and Dr. Brewer's case seemed to belong to this group, since the organism showed budding forms in the tissue. Dr. Ewing said that Dr. Coley had under observation a similar case, the material from which had been studied at the Loomis Laboratory. This included a culture of the organism which was of the budding and mycelium-forming type, and hence an oidium. The increasing number of cases reported suggested that the disease was increasing in this country, though possibly the number of reports meant merely a more accurate diagnosis. The fact that in many cases there was pulmonary involvement indicated that this disease might be more infectious than had been supposed, and also suggested to surgeons that some care should be taken in handling it. In Dr. Coley's case the entrance was apparently through a wound in the toe. This patient had a cough with some bloody sputum, but no blastomycetes had been found in the sputum. This fact suggested that the infection might be through the blood, followed by the pulmonary involvement, and from there to different parts of the body. Dr. Ewing asked Dr. Brewer if he had been able to decide how the infection occurred in his case.

Dr. Brewer said that in examining his case he had borne in mind that the greater number of cases reported so far had shown cutaneous lesions, but he had been unable to find any cutaneous lesions anywhere on this man's body, and repeated examinations had failed to show any lesions in the lungs. The case differed, therefore, from any case which he had thus far seen reported. Apparently the primary lesion was in the spine.

AN EXPERIMENTAL STUDY OF CAISSON DISEASE.

HARLOW BROOKS, M.D.

The theories which have been advanced as explanatory of the symptoms of caisson disease are very numerous. They may be quite satisfactorily grouped, however, under three heads which comprise all the more probable explanations for the symptomatology and pathological anatomy.

I. *The theory of exhaustion and cold.* This theory has been chiefly propounded by Barella, Lampardarios, Jaminet, and Woodward. Triger also endorsed this explanation to a certain extent, assuming that the pains characteristic of the disease were rheumatic in origin and nature and were the results of the marked fall of temperature which takes place during locking out or decompression. As is well known, when the air pressure is lowered in the lock a considerable amount of cold is generated, even in warm weather, and the atmosphere of the lock becomes thick with fog and intensely cold. Jaminet, Woodward, and the others assumed that the conditions following the physical exhaustion incident to the work performed in the caisson caused extreme prostration and pains rheumatic in type. They claimed that the work was more exhausting because of the more rapid tissue metabolism which they assumed to take place as a result of the increased absorption of oxygen due to the compression or concentration of the air. They concluded that the cold generated in the locking out process acted particularly harmfully on account of this unnaturally exhausted condition of the body. Though this theory has now been abandoned by practically everyone, still it may be well to state a few of the more conclusive argu-

ments against it. In the first place the disease is quite as apt to develop in men such as foremen and overseers who perform little or no physical work; and the warming artificially of the outgoing lock has not resulted in a decrease in the number of cases. Furthermore, the statement that tissue metabolism takes place more rapidly under the compressed air is largely based on the premature conclusions of Jaminet that the urinary solids are markedly increased; and he assumed, entirely without proof, that this increase in solids represented an augmentation in nitrogenous waste products. No account was taken of the excretion by the bowel or skin and the theory is not even founded on correct or demonstrated primary assumptions. Contrary to the claims of this theory, workmen assert that exertion in the compressed air tires them less than in ordinary atmospheric pressure. It has also been shown that active exercise immediately after locking out prevents or lessens the severity of the symptoms. This theory of exhaustion has received no confirmatory evidence from experimental sources, and may now be entirely discarded.

II. *The theory of congestion and its sequelæ.* This theory has received the support of some of the most eminent workers, among whom may be mentioned Pol and Wattelle, Guerard, Limousin, and Andrew H. Smith. It is chiefly founded, apparently, on the gross pathological changes found. These, as has already been noted, are largely vascular in nature, congestion and hemorrhagic softening of the spinal cord and brain being the most constant lesions reported. Pol first showed that the danger of accident lay not in the increased pressure, but in the too rapid diminution of it. That Pol was quite correct in this statement is proven by the experiments of M. Hersent of Bordeaux (*Eng. News, Vol. XXXIV,*

p. 67), who showed that the effect of excessive pressure extending up to 76.8 lbs., produced symptoms entirely different and distinct from those manifested in caisson disease; and it is now universally admitted that the rapidity of decompression is the essential producing factor. Smith states in addition that the length of time of exposure to pressure is also most important. This is doubtless true, but to a limited degree. For example, in in the Brooklyn gas tunnel several donkeys were kept under pressure for nearly two years, the pressure at times reaching as high as fifty-two pounds, which I believe is the record of high pressure under which work has actually been carried on. Some of these animals were removed from the air rapidly; all such suffered or died from caisson disease; while those animals which were locked out in the same amount of time used for the men, came out entirely free *(W. I. Ames, Eng. News, Vol. XLI, p. 27)*. This fact is of particular importance when we come to weigh the statement of Smith that long exposure of the superficial vessels to the support of the increased external pressure weakens the tone of these trunks so that on return to atmospheric pressure the vessels are unable to sustain the pressure of the normal blood. While it is beyond question true that during compression and also decompression considerable unbalancing of the circulatory function takes place, still that this is sufficient to cause the anatomical changes found post mortem has not been satisfactorily demonstrated. Finally, I have shown by the accurate determination of the blood pressure in a considerable number of cases, before, during, and after exposure to the increased atmosphere in the caisson, that but slight alteration in arterial pressure takes place, and, in so far as can be determined by our most accurate methods, the cardiac energy is

neither augmented nor decreased. It is manifestly impossible that any considerable difference can exist between the pressure within the body and that without, for were this the case collapse of such cavities as the abdominal must necessarily follow, a fact very well illustrated by tears of the membrana tympani where the Eustachian tube is imperforate. Catsario, from his experiments and observations, concludes that barometric pressure has no direct influence on the liquids in an organism, and an equilibrium of pressure exists throughout entire masses of blood. I feel that we are now quite safe in assuming that, after the tissues have become accustomed to the increased atmospheric pressure, say in twenty to forty minutes, no serious disturbance of the vascular distribution takes place, and we must look for some other explanation for the congestion and hemorrhage admittedly characteristic of caisson disease.

III. *The gaseous theory.* Briefly, this theory assumes that the blood, or the blood and tissues of the body take up an increased amount of air or gas proportionate to the amount of external pressure, which is liberated when the pressure is diminished. This theory in some of its forms has received the sanction of Bert, Boyle, Cassant, Catsario, Feltz, Francoise, Hoppe-Seyler, von Leyden, and many others. Bouchard attempted to explain the condition by the theory of compression of the intestinal gases, which acting like a great cup draws the blood from the other parts of the body, producing local anemia. This fanciful explanation I think does not even require discussion. Most of the observers believed that the increased gaseous content was due to absorption to a balanced point in the abnormally dense surrounding air. Boyle showed, by rapidly exhausting the air about animals confined in the chamber of the air pump, that bubbles of

gas formed in the blood and tissues, and that these animals died much more rapidly than animals simply deprived of oxygen. Hoppe-Seyler from similar experiments concluded that death was caused by pulmonary air emboli in these experiments and that the offending gas in caisson disease was largely or entirely oxygen. Bert, from experimental and clinical studies, accepted this doctrine, except that he assumed that the gas thus set free on decompression was nitrogen and not oxygen. In this relation we must consider Dalton's law, that the weight of a gas dissolved by any given fluid at a given temperature is directly proportionate to the pressure that the free gas exerts on the fluid. Assuming this to be equally true with the human body under compressed air, release from its excessive external pressure will naturally be followed by the liberation within the body of a bulk of air commensurate with the difference in pressure existing in the caisson and in the external atmosphere, and we should then expect bubbles of free air to be found within the tissues of the body under such circumstances.

The experiment of Smith which tends to showt hat the quantity of air absorbed by the blood is quite insufficient to produce serious changes in the body is invalidated, in my opinion, by the fact that he examined the blood alone, whereas in life all the tissues of the body are practically immersed in fluid. The earliest observations tending to substantiate this proposition are those of Heiberg (*Gazette med. de Paris, 1878*). In Heiberg's case, as also in one of Pol's cases the presence of gas blebs might be explained by post-mortem infection with such an organism as the B. aerogenes capsulatus. As already stated, however, Boyle, in 1670, produced bubbles of gas within the blood by rapid exhaustion of

air with the air pump. Francoise had suggested this possibility in 1860, after a study of his cases. Compliance with Dalton's law probably explains the variation in the rate of occurrence of caisson disease under the same pressure but with varying barometric conditions.

Bert, Catsario, and many others have confirmed these observations experimentally, and those of you who are familiar with the appearance of acute cases of caisson disease, either in vivo or at early post-mortem, are, I think, quite willing to accept the statement that such a liberation of free gas in the fluids of the body not only could, but does exist without causing air emboli and death in every instance. This is readily explained by the fact that the human body can withstand large quantities of air or nontoxic gas so introduced, as shown by the experiments of Magnin, Connoly, Feltz, Petit, Demarquery, and many others. This statement has been rather recently substantiated by experiments on air emboli conducted by Crile. Therefore, some explanation, aside from the mere presence of gas bubbles within the body must be supplied. Ames and others above mentioned attempted to explain this by the entirely untenable statement that carbonic dioxide poisoning results from the liberation of this gas, and that this toxemia is really accountable for the symptoms of caisson disease.

Bert asserted that nitrogen poisoning resulted from the liberation of this gas, while others have considered the symptoms due to excessive oxygen liberation. The symptoms and lesions produced, however, correspond to none of these toxemias, and the true solution was found by von Leyden in 1879. In the study of a spinal cord from a case of caisson disease, this scientist found minute lacerations of the substance associated with rupture of the small vessels, both of which changes he assumed to

be simply mechanical, due to the liberation of air bubbles in the tissues of the body. That lesions of this character, minute as they are, are quite sufficient to cause death when they occur in the brain or cord is, I think, beyond question. That they set up serious secondary inflammatory and degenerative processes in these organs which might thus act, appears to me entirely probable, and with a view to the demonstration of these lesions in caisson disease, I have performed the following experiments.

Experiment I. A strong flask containing 100 c.c. of distilled water was taken unstoppered into the compressed air lock. The pressure was then raised to 31 lbs., when the previously open bottle was tightly corked. The pressure was then slowly released and had fallen to five pounds above atmospheric when the cork was forcibly driven from the bottle. This experiment was repeated several times with the same result.

Experiment II. An egg and the body of a dead guinea-pig were taken into the lock, and the pressure was raised to 31 lbs. They were then placed in separate basins of water. During decompression, bubbles of air appeared on the surface, bubbling up through the water.

These simple experiments apparently demonstrate that under ordinary engineering pressures, sufficient air is released on decompression to indicate a considerable degree of absorption under pressure, by water and by the tissues of an egg or the dead animal body.

Experiment A. Three guinea-pigs, each weighing about 285 grams, were selected. Pigs A^{I} and A^{II} were killed with chloroform at the same time and in precisely the same manner.

Pigs A and A^{I} were placed in the chamber of an air pump, A^{I} being dead; and the air was exhausted rapidly so that in two minutes the mercury column stood at

25 mm. It was maintained at this height for two minutes, and then the air was admitted as rapidly as possible. After the first few strokes of the pump, pig A began to show signs of distress, running rapidly about; and very shortly both animals showed marked distention of the abdomen and to a lesser degree of the thorax as well. At the expiration of one and a half minutes, pig A threw himself on his back and with a few somewhat opisthotonic contractures ceased to breath. Meanwhile the distention of both animals was seen to be lessening rapidly. As the air was rapidly admitted, both pigs collapsed to much less than their normal bulk, and on removal from the receiver this condition still persisted.

Post-mortem examination of pigs A and A^{I} showed no apparent difference in the bodies or viscera. There was superficial anemia in both and the internal viscera were somewhat congested. No bubbles of air were found in any part of the bodies. The membranes of the brain showed a slight congestion, no greater in one than in the other.

Post-mortem examination of pig A^{II}, which had been killed simply with the chloroform, showed a slightly less degree of internal congestion.

The brains and spinal cords (inclosed in the vertebræ) of the three pigs were then placed in 5 per cent. formalin. The tissues remained in this for two days; they were then transferred to 80 per cent. alcohol, in which they remained for eight hours, when they were changed to 95 per cent. alcohol, in which they were allowed to remain for twelve hours. Small segments of the tissue were then selected and transferred to absolute alcohol in which they stayed for two and one-half hours. They were then transferred to chloroform for two hours, to chloroform saturated with paraffin for two hours, and

then to 52° paraffin for one hour. Sections were then blocked, mounted, and stained in the usual manner, the stains used being hematoxylin and eosin.

The brain from pig A showed quite marked dilatation of the blood and lymph passages, though for the greater part they were empty. The perilymph spaces were everywhere exaggerated, and in the white matter, notably in the internal capsule, there had apparently been an exudate of lymphocytes and polynuclear leucocytes between the nerve fibrils. The blood vessels seemed to be in a normal state as to the blood content. No air vesicles were present and no evidence of tissue laceration other than the widening of the perilymph spaces.

Sections of the spinal cord from pig A showed no alterations in the gray matter. The blood vessels were not congested; on the contrary, they seemed somewhat sparingly supplied with blood. The white matter showed quite frequent air vesicles, oval or circular in outline, and situated between nerve fibers, which had apparently been displaced. There was no apparent surrounding inflammatory reaction, and, for the greater part, these vesicles seemed to be empty, but a few contained small quantities of a serous exudate. The lesions were most frequent in the upper lumbar portions of the cord and in the anterior columns, along the anterior median fissure particularly. That these changes were not artefacts was apparently indicated by the fact that the nerve cells were not shrunken, and when stained by the Nissl method showed normal cytoplasmic pictures. Furthermore, the epithelial lining of the ventricle of the cord was intact and showed cilia very distinctly.

Section of the brain from pig A^1 showed practically

the same appearances as those seen in A, except that the distention of the perilymph spaces was less apparent.

Sections of the spinal cord of pig A^{I} showed a normal structure throughout the cervical region, but in the lower dorsal and lumbar regions, the presence of air vesicles, particularly in the anterior columns, was shown. The degree of these was apparently not so great as in pig A; that is, the vesicles present were not quite so large and possibly not quite so numerous. Sections stained by the Nissl method, as well as those prepared in the ordinary way, seemed to indicate the absence of artefacts of any serious degree.

Sections of brain from pig A^{II} showed a normal condition. The vessels were less congested than in the two previous specimens, and the distention mentioned in the perilymph spaces was not apparent. The sections were compared closely to the previous ones.

Sections of the spinal cord from pig A^{II} did not show the presence of air vesicles, described in A and A^{I}. Areas were of course present where the tissue had undergone more or less mechanical distortion, but the large spaces noted in the other cords were not seen.

Experiment B. Three guinea-pigs, each weighing 250 grams, were selected, all as much alike as possible. Pigs B and B^{II} were killed with chloroform in the same chamber at the same time.

Pigs B and B^{I} (B being dead) were placed in the receiver of the air pump and the air was slowly exhausted so that at the end of four minutes the mercury stood at 45 mm. The dead pig swelled somewhat, the living one considerably less. The breathing of the living animal became quite rapid and somewhat stertorous; after six minutes he fell on his side with the abdomen somewhat distended, still breathing rapidly.

The column of mercury was kept at the same level for eight minutes, the animal remaining apparently in the same condition, but the abdominal distention becoming less and less. Finally, the air was admitted quickly (15 seconds), and the animal, still breathing rapidly, was removed. After five minutes the animal began to attempt to rise, opened its eyes, and at the end of ten minutes seemed to be perfectly normal. About one hour later, the animal began to breathe rapidly and evidently with considerable effort; later it improved, but four hours after was not yet entirely normal.

The tissues from pigs B and B^{II} were examined. There was a marked congestion apparent in the viscera of pig B, less marked in pig B^{II}. The brains and spinal cords were removed and placed in 5 per cent. formalin, the cord, as before, being still inclosed in the column. The living animal recovered completely, being entirely normal on the next day.

The tissues B and B^{II} remained in 5 per cent. formalin for forty-eight hours, when they were removed to 80 per cent. alcohol, after which the vertebræ were carefully cut away. After twelve hours they were transferred to 95 per cent. alcohol for six hours, and to absolute alcohol (small blocks having been selected) for four hours; to chloroform, three hours; chloroform paraffin, two hours; and 52° paraffin for twelve hours. Good sections were obtained and were stained with hematoxylin and eosin. Throughout the process the two groups of tissues were handled in precisely the same manner.

Selections from the brain of the control animal B^{II} showed no shrinkage of the ganglion cells or other artefact. Blood vessels were moderately congested. The spinal cord from the same animal showed no change,

with the exception of slight laceration caused by an improperly sharpened knife.

The brain from pig B showed no observable changes. Blood vessels were for the most part empty or contained but scant amounts of blood. Apparently they were contracted. There was no ganglion cell shrinkage and nothing to indicate artefacts.

The spinal cord from the same animal appeared to be perfectly normal. In the lumbar portion there were a few vesicles between the nerve fibers and the same were present in less degree in the lower dorsal.

Experiment C. October 15. Two guinea-pigs were selected, C weighing 250 grams, and C^1, 400 grams. Both were placed in the chamber of the air pump and the air was quickly (one minute) exhausted to 20 mm. where it was held for one and a half minutes. Both animals inflated rapidly, breathing became fast, and after one-half minute both keeled over, still kicking and struggling somewhat. The air was then admitted rapidly and the pump was started to remove the CO_2 and to force in fresh air. After five minutes both pigs revived and were able to stand. The vent was then closed and the air was again exhausted as before; but inflation of the bodies was much less apparent and the animals evidently suffered but very little, not losing station or consciousness. They were kept in this partial vacuum at 20 mm. for two minutes, when the air was again rapidly admitted. Collapse of the bodies immediately took place, but five minutes after removing them from the chamber they walked about and appeared to be free from pain; but twitching of the extremities was present in slight degree and some time elapsed before they seemed to be in perfect mental equilibrium.

October 16. Same experiment repeated with the

same result, the animals having been apparently in good condition in the meantime.

October 17. Same experiment; twitching more marked; lack of inflation at second aspiration marked. Recovery slower than on October 15 or 16.

October 18. Same experiment; both animals much exhausted after last aspiration. Abdomen collapsed on admitting air. Slight convulsive seizures on aspiration second time. Much exhausted, but revived after removal from chamber.

October 19. Animals sick since October 18. Experiment repeated; both much exhausted; breathing very rapid and convulsive after removal from chamber. The animals were not seen on October 20. They were active on the night of October 19.

October 21. Animal C (smaller) found dead. Internal organs congested; apparent rupture of the stomach as from a tear. Post-mortem changes general but of moderate degree. The brain and cord were removed and placed in 5 per cent. formalin, later carried through alcohol and so on as before. Animal C^1 was evidently sick; its hair was ruffled; it squealed if handled, and did not eat well.

October 23. Animal C^1 still sick; killed by chloroform; no gross lesions of internal organs. Tissues put in 5 per cent. formalin; technique as before. The animal was apparently better on October 22 and 23, but was still not well, and the action of the rear extremities seemed faulty.

Specimens were prepared for microscopic examination by the method before detailed, and in association with the organs of a control normal guinea-pig.

Animal C showed dilatation of the lymph spaces of the brain and cord. Occasional air vesicles were found,

particularly in the neighborhood of the blood vessels, but the specimens exhibited sufficient post-mortem changes to cause artefacts.

The brain of animal C^{I} showed moderate congestion of the blood vessels. There was a slight leucocytic infiltration of the pia-arachnoid, and some of the blood vessels showed slight perivascular softening with small hemorrhages and edema. Recent karyokinetic changes were presented in the walls of some of the blood vessels. There was a general dilatation of some of the perivascular lymph spaces throughout the brain.

The vascular changes were more pronounced in the cord than in the brain, particularly in the dorsal and lumbar levels. Open spaces, apparently representing air vesicles, were found from place to place and were surrounded by areas of necrosed tissue. No ganglion cell changes were evident.

These experiments apparently show that when the air about either a living or a dead animal is quickly exhausted, air vesicles appear in the central nervous tissues, especially in the white matter of the spinal cord, associated with dilatation of the lymph spaces. Since these changes take place, though in slightly less degree, in dead tissues, it is fair to assume that they are mechanical in nature. The absence of lesions in control animals, the tissues of which were prepared in precisely the same manner, excludes the possibility of artefacts.

The symptoms produced by rapid exhaustion of the air are very similar to those of caisson disease, though complicated in these cases by deficiency in oxygen and the presence of CO_2.

The swelling of the bodies, both of the living and of

the dead animals, on lowering the pressure, and their collapse on return to normal, shows that the pressure within the body corresponds to and varies with that of the surrounding atmosphere.

Experiments indicate that most of the symptoms evinced on rapid exhaustion of the air are due, not to abstraction of air *perse*, but to the effects of changes in the external and internal air pressure.

Frequent decompression from normal atmospheric pressure causes symptoms indicative of disease of the brain and spinal cord, and the appearance in these tissues of lesions of an inflammatory character, manifested by proliferation of the vessel walls, perivascular edema and necrosis, dilatation of the lymph spaces, occasional minute hemorrhages, and the formation of air vesicles, most numerous in the spinal cord; in brief, myelitis.

Experiment D. Two animals were selected, a small sized rabbit, animal D, and a guinea-pig, weighing 250 grams, animal D[1]. The animals were placed in the air chamber and compressed air was slowly admitted until at the end of eight minutes the pressure was 75 lbs. above atmospheric. The pressure was maintained at this level for sixteen minutes. The air was then allowed to escape rapidly (from 75 to 0 lbs. in one minute). The animals were removed from the chamber two minutes after release of pressure. Both were apparently in good condition and showed no evidence of suffering or disturbance. They remained in this normal state for three minutes, when the rabbit (D) suddenly became excited; breathing was rapid; and in one minute convulsive tremors of the lower extremities were noted. After

ten minutes there was paralysis of the hind extremities, more marked on the left side.

Animal D^1 began to breathe a little rapidly about five minutes after removal from the chamber, but apparently recovered shortly.

Four hours later animal D had apparently fully recovered. Slight disability of the left rear extremity could be detected on careful examination, but otherwise it seemed normal.

Both animals were killed by chloroform, and the tissues were placed in 5 per cent. formalin, then transferred to 80 per cent. alcohol, and handled as before.

Animal D (rabbit). The brain showed general dilatation of the perivascular lymph spaces. The blood vessels were generally congested. There was an occasional occurrence of air vesicles, particularly in the white matter, seen most distinctly where longitudinal sections of fibers were presented. Artefacts were excluded by control. There was marked dilatation of the perivascular lymph spaces. A few of these vesicles were apparently filled with lymph and a fine detritus. Others of them showed a probable relationship to the blood vessels and still others were surrounded by edematous and slightly lacerated tissue.

Animal D^1 (guinea-pig). The brain showed leucocytic infiltration with hemorrhage per diapedesis and small areas of necrosis and edema about some of the cortical and meningeal trunks.

The spinal cord showed vascular changes similar to those indicated in the brain. Occasional air vesicles were seen especially in longitudinal sections of the fibers. There was marked dilatation of the perivascular lymph spaces. The pericellular spaces in some instances showed enlargement from air vesicles.

Experiment E. Animal E was a small sized rabbit, animal E[1] a guinea-pig weighing 250 grams. The animals were placed in the chamber and the air was slowly admitted (six minutes) until the pressure reached 55 lbs., above atmospheric. The pressure was maintained at 55 lbs. for thirty minutes. The air was released in one minute. The animals emerged from the chamber apparently normal. After five minutes the rabbit began to breathe rapidly and convulsive tremors of of the body were inaugurated; slight paralysis of the rear extremities resulted. The guinea-pig was apparently unaffected.

The animals were killed after fifteen minutes, by chloroform. No congestion of the superficial or internal organs was apparent. There were no gross lesions of the spinal cord or of the brain. The tissues were placed in 5 per cent. formalin and treated as before.

There was marked congestion of the vessels in the brain and cord of both animals with occasional hemorrhages of minute size, and dilatation of the lymph spaces. Air vesicles were present in both the brain and spinal cord, as in the specimens in *Experiment D*, but were less numerous and smaller.

Experiment F, November 12. Two rabbits, F and F[1], together with two guinea-pigs, 'f' and 'f'[1], were placed in the air chamber. The pressure was raised from 0 to 75 lbs. in four minutes. Owing to leakage this was diminished to 60 lbs. in ten minutes. The pressure was released in thirty seconds. The animals were removed from the chamber after one minute, and were found apparently normal, except that the urine had been passed. After three minutes the animals began to show signs of distress, rapid respiration, trembling and staggering gait. At the end of ten minutes they had

apparently recovered. The vessels of the ears of the rabbits were of about normal size, though at first rather congested.

At the end of ten minutes the animals were replaced in the chamber and the pressure was raised to 60 lbs. in one and one-half minutes. They were kept at this pressure for fifteen minutes, and locking out was completed in thirty seconds, the animals being exposed in one and one-half minutes.

When first removed the animals showed no changes, but almost immediately the two guinea-pigs began to have rapid twitching of the extremities and rapid respiration, and finally, paralysis of the rear extremities. The rabbits a little later showed similar symptoms, but of more marked degree. Recovery began in fifteen minutes, and three hours later all appeared comparatively well except that the hair was rough and handling was evidently painful, and the tendon reflexes were greatly increased. The condition of the ear vessels were closely observed. Immediately after removal there was a congestion of the veins; this gave way to an arterial hyperemia; but after five minutes the vessels seemed to be normal.

November 13. All the animals were found in apparently normal condition. The tendon jerks of the rabbits were somewhat increased, but otherwise they seemed natural. Ate normally.

November 14. Animals in normal state. Rabbit F and guinea-pig 'f' transferred to *Experiment G.* Rabbit F^1 transferred to *Experiment H.*

Experiment G, November 16. A large rabbit, F, and a medium size guinea-pig, 'f', were placed in the air chamber, and compressed air was admitted up to 45 lbs., two minutes being occupied in locking in. The pressure

was maintained at this point for two hours. Locking out was accomplished in thirty seconds, and the animals were exposed in one and one-half minutes. The guinea-pig gave a few convulsive twitches, voided the urine, and died immediately, the abdomen inflating considerably. The rabbit was very cold, and soon began to have a swaying gait, terminating in partial paralysis of the rear extremities. He had rapid breathing and shook and voided urine and feces. The ears were very cold and almost bloodless. He remained in this condition for ten minutes when he began to show slow signs of recovery, finally breathing regularly and regaining the power to walk though at the end of fifteen minutes the gait was still very uncertain. He was then returned to the cage with the other animals.

At the post-mortem on the guinea-pig the superficial vessels were found to be anemic, while the internal viscera were congested. The cord and brain were removed and placed in 5 per cent. formalin; neither was congested, though the liver, kidneys, and spleen were.

Histological Summary. The brain showed numerous, very large sized air vesicles, apparently representing the greatly distended lymphatics and the perivascular lymph spaces. Some of the vessels showed proliferation of the endothelial lining. No ganglion cell changes were evident. In the cord the dilatation of the perilymphatic spaces was especially marked about the ganglion cells of the anterior horns.

The tissues were transferred to 80 per cent. alcohol and later treated after the usual manner for paraffin sections.

November 17. Rabbit F still showed marked increase of knee jerks, but ate well. No paralysis was evident.

Experiment H, November 14. Rabbit F^1 and a normal rabbit H, selected as of about the same size and weight, were placed in the air chamber. The air was admitted fairly rapidly so that at the end of three minutes the pressure stood at 70 lbs. Communication with the air tank was cut off. Leakage was slight, but the pressure fell somewhat and at the end of fifteen minutes the communication with the tank was again established to permit dilution of CO_2; this process was repeated four times during the hour and the pressure was maintained almost constantly at 70 lbs.

After an hour the air was permitted to escape rapidly, so that the pressure fell in thirty seconds from 70 lbs. to 0. The animals were removed from the chamber in one minute from beginning of locking out. They were found in a condition of collapse; the bodies somewhat inflated, skin cold, large quantities of urine voided; temperature of chamber low. On removal from the chamber the ear vessels were very anemic, almost bloodless, and the animals showed convulsive seizures. They were not paralyzed, but suffered from tremors, evident dizziness and ataxia. After five minutes complete paralysis of the rear extremities had taken place, and a little later paralysis of the fore extremities. The animals lay helpless; the breathing was very rapid and shallow; the heart action was rapid and irregular.

At first the ear vessels were very anemic. This condition was soon followed by a very marked congestion which lasted but a few minutes, being replaced again by a very marked anemia with coldness. These vascular changes continued throughout the forty-five minutes during which the animals were closely observed. The changes from extreme anemia were more marked in rabbit F^1, though they were also very apparent in H. The

waves of vascular alteration were not the same in the two animals, but each phase lasted usually from a few seconds to two minutes. The condition of absolute paralysis passed somewhat and the animals were able to use the fore extremities. In the rear extremities paralysis remained complete, and the mental condition apparently became steadily worse. Both animals had very cold skin, were unable to hold their heads up, and showed frequent convulsive seizures with spasms of twitching.

At the end of forty-five minutes from locking out, animal H was killed by a few whiffs of chloroform, as it was seen that recovery was impossible; respiration had become irregular, great vascular alterations still persisted, and the heart action was rapid. As soon as possible the spinal cord together with the brain was removed. The internal viscera were considerably congested; no air emboli were evident; and the dural vessels of the cord were very markedly congested; but though there were apparently areas of softening in the spinal cord, no spinal hemorrhages were macroscopically demonstrated. The vessels of the brain were moderately congested, and no areas of softening were evident.

The tissues were immediately placed in 5 per cent. formalin and were subsequently handled after the usual method.

One hour after locking out, animal F^1 was found to be dying. As soon as respiration had ceased the tissues were removed after the usual method, and were found to show exactly the same conditions seen in animal H. Tissues of this animal were handled in the same manner as those of H.

No provisions were made in this experiment for the disposition of CO_2, except that the communication with the entire tank of compressed air was frequently

opened. As animal F in experiment G had recovered from similar conditions it was thought that the amount of CO_2 did not influence the result to any appreciable degree.

Experiment I, November 25. Rabbit F, together with a smaller rabbit I, was placed in the compressed air chamber, and the pressure was increased from 0 to 60 lbs. in one minute. The pressure was maintained at that grade for forty-five minutes, frequent communication with the entire tank being opened for dilution and CO_2 poisoning. Further, an abundant supply of fluid NaOH was placed in the chamber. The air was released rapidly, the pressure falling to 0 in thirty seconds, and one minute was taken in releasing the animals. The animals were removed from the chamber in a dazed condition, and in a few minutes paralysis of the extremities and of the back was marked, and the breathing rapid. The ears became rhythmically congested and anemic, the animals were very much distressed, and at times spasmodic trembling of the entire body took place. These symptoms continued for three hours, becoming then slowly less marked and finally disappearing on the next day, though the animals were not well. The large animal showed the less pronounced symptoms.

November 27. The animals were apparently well, and the experiment was repeated in all details, except that the maximum pressure was 45 lbs. Symptoms were less marked and the paralysis was more pronounced in the fore extremities. Recovery was more rapid than before, but animals were profoundly affected.

December 2. Rabbits F and I were placed in the chamber and pressure was raised from 0 to 90 lbs. in six minutes. The animals were left in this pressure for thirty minutes. The pressure was then gradually diminished by allowing the slow escape of the air, so that in ten

minutes it had fallen to 0. The animals emerged from the chamber apparently undisturbed, and showed no symptoms either then or later which would tend to indicate that the pressure had been at all deleterious.

December 5. The animals had remained in a normal condition, and both had gained in weight. Both animals were placed in the chamber, and the air was slowly admitted so that at the end of six minutes the pressure had risen from 0 to 110 lbs. The pressure was maintained at this point for sixty minutes, The air was then permitted to escape very rapidly, so that in thirty seconds the pressure had become 0. The chamber was opened one minute from the end of the locking out. The animals stepped from the chamber as though in normal condition, except that the breathing was not as slow or regular as natural. They walked about the room, appearing to be somewhat excited, but not showing any signs of paralysis. At the expiration of three minutes, the animals almost simultaneously became very much excited, and the ears became pale. Previous to this they had alternately paled and flushed, but this was much less marked than in the previous experiment.

The pupils were distended, the eyes bulged from the head, and the head was thrown rhythmically from side to side. The neck muscles stiffened; spasmodic twitchings of the rear extremities came on followed by paralysis, apparently beginning from behind and extending forward; finally paralysis involved all of the extremities, and the animals fell to the floor. The action of the heart was irregular and weak. The smaller animal succumbed first and was dead in five minutes from the beginning of serious symptoms; while the larger animal lived slightly longer and died suddenly, giving forth cries.

As soon as the animals were certainly dead the cavities were opened and it was at once noted that the vessels of the omentum and mesentery were much congested. In the smaller animal they contained numerous bubbles of air, while the subcutaneous tissues were also emphysematous to a moderate degree. The subperitoneal fat, particularly that about the kidneys, was riddled with gas blebs, and the peritoneal coat of the gut in many places was raised into tiny blebs. The entire gut was considerably distended but no ruptures had taken place. The lungs were very emphysematous, particularly in the smaller animal. The cord and brain showed no gross lesions. The liver was congested in both cases, but no emphysema of this organ was evident. There could be no doubt as to the presence of air bubbles in the tissues and blood vessels, and when the trunks were cut the blood which escaped from them was literally red foam.

The brain and spinal cords were removed in the usual manner and at once placed in 5 per cent. formalin, where they remained for twenty-four hours. They were then gradually removed to 80 per cent. alcohol, remaining in this for twenty-four hours. The spinal vertebræ were removed, and after having been again placed in 80 per cent. alcohol, the cords and brain were segmented and the portions chosen for examination were transferred to 95 per cent. alcohol for eighteen hours, after which they were placed in absolute alcohol for three hours, transferred to chloroform for six hours, chloroform saturated with paraffin for eighteen hours, and paraffin for three hours. They were then sectioned.

When these sections were blocked it was found to be very difficult to remove the bubbles from the specimens, which behaved exactly as specimens of lung tissue when handled in the same manner. For this reason the tissues

were reblocked several times. The result, however, was bad in each case and the sections obtained were not as smoothly cut as was usually the case. For this reason, and because the lesions found in these specimens led me to think of possible errors of technique which had given rise to very pronounced artefacts, I carried other blocks of the same tissue through collodion, in a similar manner, using the greatest care to avoid artefacts, the tissues being allowed to remain in absolute alcohol and in thin collodion but a very short time. As the lesions found in both sets of specimens were identical, I am justified in the conclusion that the changes were not brought about by faulty technique in their preparation.

Rabbit H. Microscopic Examination. The brain showed marked dilatation of the lymph spaces. There were a few microscopic areas of hemorrhage in the meningeal or cortical vessels, and very marked dilatation of the perivascular and pericellular lymph spaces. Many of the vessels were markedly contracted. No ganglion cell changes were present. The spinal cord showed perivascular and vascular changes like those in the brain. The alterations were apparently most marked in the dorsal levels.

Rabbit F showed no changes exactly like those detailed in rabbit H, except that in addition to dilatation of the lymph spaces and minute hemorrhages into the air vesicles, many of the smaller trunks were surrounded by leucocytic infiltration and by more marked edematous and necrotic changes in the tissues; and the endothelium of certain of the vessels showed marked proliferation.

Rabbit I. The brain showed changes noted in the other animals, but to even more marked degree, in addition to interstitial hyperplasia about certain of the vessels.

Experiment J. A medium size rabbit was placed in the air chamber, the usual precautions being taken to prevent CO_2 poisoning. The pressure was raised in six minutes from 0 to 100 lbs., at times rising to 110 lbs. This pressure was maintained for 45 minutes, at the end of which time the air was allowed to escape slowly so that at the end of ten minutes the pressure was 0. The animal emerged from the chamber apparently unaffected and continued in normal condition.

Conclusions.

The conditions existing in the production of true caisson disease have been closely simulated in my series of compression experiments with, however, the omission of physical exercise. The fact that the resulting state closely resembles true caisson disease indicates then that exertion or physical exhaustion is at least an unessential factor in its production.

In all the hyperpressure experiments the stage of compression or locking in was productive of no serious symptoms or lesions, even when the pressure extended up to the enormous figure of 110 lbs. above atmospheric *(Experiments I and J).* In human beings, however, it is doubtless true that these excessive pressures can not be endured, as demonstrated abundantly in practical work as well as by the experiments of Hersent, only one of whose subjects was able to sustain the pressure of 76.8 lbs.

The length of time under pressure appears to be an important factor in the production of the disease, as first stated by Smith, and indicated especially by *Experiment G.* This is probably accounted for by the more complete absorption of the compressed air, and

consequently the greater difficulty in liberation on decompression.

Serious or fatal symptoms appear only on too rapid decompression, and this appears to be the one absolutely essential factor in the production of the lesions. This is especially indicated by comparison with the exhaustion experiments *A*, *B and C*. This observation is in thorough accord with the best clinical statements in regard to this important fact.

The condition of the air of the compression chamber appears to furnish no essential agents toward the production of the disease. In practice this can, however, be but partly true, for unquestionably the presence of CO_2 in excessive amounts, or of such foreign materials as illuminating gas, fire damp, and soot, as found in the early caisson work, in the first use of the diving bell, and of course where free oxygen is deficient, causes secondary depressing conditions which can not fail to have a great clinical bearing.

The essential anatomical lesions found in both acute true and acute experimental disease are identical. They consist of dilatation of the lymph channels, the presence of free air vesicles or lacerations resulting from the liberation of air in the vessels and in the soft tissues, notably in the spinal cord and brain, and of capillary hemorrhages. Hemorrhage per rhexam has never to my knowledge been reported in caisson disease.

Exactly similar changes, varying only in degree, are produced by rapid exhaustion of the air, thus excluding the theory of gas toxemia. My experiments (*A*, *B and C*) in this research thus substantiate thus performed by Boyle in 1670. These lesions are produced alike in the living and dead body; they are, therefore, probably mechanical and not pathological in origin (*A*, *B and C*).

Air under compression is absorbed by inert fluids (*Experiment 1*) by certain inert tissues (*Experiment 2*), and by dead and living animal tissues (*Experiments A to J*), and the amount of absorption depends largely on the degree of compression, probably complying with Dalton's law. On release of the pressure, air is liberated from these substances in quantity according to the degree of previous absorption (*Experiments D to I.*)

When rapid liberation takes place in dead or living animal bodies, it causes the dilatation of the lymph passages, the rupture of capillaries, and the production of tissue laceration by the escaping air bubbles. Frequent repetition of these lesions in the living tissues causes endothelial and interstitial proliferation in and about the diseased vessels and eventually secondary inflammatory changes. (*Experiments C, H and I.*)

The symptoms of true caisson disease admit of the above causative explanation, and the paralysis and symptoms of spinal and cerebral disease are produced in this manner. They are followed in subacute or chronic cases by secondary degenerative and inflammatory lesions which may be grouped as myelitis (*autopsy reports*).

Finally, from the pathology of true and experimental caisson disease, we are justified in concluding that the essential productive factor is the rapid liberation of air from the fluids and tissues of the body when decompression is allowed to take place too rapidly. This liberation of bubbles of air causes laceration of the soft tissues, dilatation of the lymph spaces, and capillary hemorrhage.

Discussion.

Dr. O. H. SCHULTZE said that he thought all would subscribe to Dr. Brooks' conclusion that the primary

cause of death, where this occurred after coming out of the caisson, was too rapid decompression. In speaking of the presence of gas in the body, Dr. Schultze said that he had seen cases at autopsy where the right ventricle was so distended that on opening the heart under water there was an ebullition of gas which practically amounted to an explosion. In one case, at least one-third of the contents of the right ventricle was gas. The lungs in some cases showed very intense congestion; in other cases, where there was a large gas content in the right ventricle, the lungs were extremely pale and emphysematous. The cases varied considerably in regard to the amount of cellular emphysema which occurred. The first case which Dr. Schultze had autopsied had shown a very marked cellular emphysema in the appendices epiploicæ. In cases dying several hours after decompression or perhaps one or two days after, in which event no gas would be found in the blood, the cause of death might be difficult to determine. In two cases which he had seen, the examination of the spinal cord showed small hemorrhages scattered throughout the cord, and this might explain why some of these patients later develop paraplegia. In regard to the ecchymoses which were occasionally seen, these might be due to the mode of death. In one case which Dr. Schultze had examined, of death following too rapid decompression, both middle ears were filled with blood. This evidently was a case where there was a direct rupture of vessels.

Dr. A. Wadsworth asked Dr. Brooks whether in the lesions which he had examined there were any signs of the liberation of gas within the cells.

Dr. Brooks said that he did not know. He had been so sceptical about artefacts, that he had not felt sure whether many of the findings were due to the effects

of the air or whether they were artefacts. He had performed personally only two autopsies on cases of human caisson disease. Both of these had died of pulmonary embolism. He had thought the embolism in these cases was probably due to softening of the spinal cord.

ON THE INFLUENCE OF TISSUES, CHOLESTERIN AND CHOLESTERIN ESTERS UPON THE PRODUCTION OF TETANOSPASMIN AND TETANOLYSIN IN FLUID CULTURES.

HIDEYO NOGUCHI, M.D.

In an anaerobic culture of B. tetani, tetanospasmin and tetanolysin develop simultaneously. The amount of lysin in such cultures is, as a rule, small when compared with the amount of spasmin, and can be disregarded in the fatal issue which follows tetanus intoxication. But, so far as I am aware, there has been no direct evidence brought out for this assumption, and a separation of tetanospasmin and tetanolysin in a culture of B. tetani has never been effected. In the present study I have succeeded in obtaining a culture, which, while rich in spasmin, possessed no hemolytic principle. The experiment also may illustrate the mode of the toxin production of B. tetani in the animal body. I have cultivated B. tetani in bouillon containing portions of fresh or boiled animal tissues, and cholesterin or various esters of cholesterin, and have then examined them for these two active principles. The result can be summarized as follows:

The addition of fresh or boiled tissues. To ordinary plain or 0.5 per cent. glucose bouillon, a small portion of sterile organs (liver, spleen, kidney, of rabbit or guinea-pig) was added. Two series were prepared, one raw and the other boiled for five minutes before inoculation with B. tetani. After inoculation, the two series were cultivated both anaerobically and aerobically at 37° C. for two weeks. The controls, with plain or glucose bouillon, but without the addition of tissues, were cultivated anaerobically.

Growth was abundant in tubes with tissues, and less in the controls. Microscopically, there were numerous spores in the former, but almost none in the latter.

Examination for toxicity and hemolytic power was made. Rats were employed for the determination of toxicity (subcutaneous), and the washed corpuscles of the rabbit for the lysis. The minimal lethal dose of the control cultures was found to be 0.001 c.c., and the minimal dose for complete hemolysis for 2 c.c. of a 5 per cent. suspension of the washed blood corpuscles, 0.04 c.c. The toxicity of the anaerobic cultures of tissue bouillon (both raw and boiled), was 0.001 c.c.; that is, exactly the same as the controls; but none of the tissue cultures exhibited hemolytic activity.

The bouillon culture containing tissue grew aerobically just as well as the anaerobic series, and formed numerous spores. The toxicity of the aerobic culture was, however, decidedly inferior to the anaerobic. It required 0.1 c.c. to produce death in six to eight days; but 0.01 c.c failed to kill the animal although it produced marked tetanus and subsequent exitus from emaciation after a long period (thirty days in one case.) No hemolysin developed in the aerobic cultures with tissues.

The addition of cholesterin and cholesterin esters. Cholesterin (Merck) and its various esters, including palmitate; stearate, and oleate, as prepared after the method given by Hürthle, were employed. None of these preparations is soluble in bouillon. Cholesterin and

cholesterin palmitate can be suspended fairly evenly, but after long standing sink to the bottom of the vessel. Stearate and oleate of cholesterin are higher and float to the upper layer of the fluid. Four-tenths (0.4) of a gram of each preparation were mixed with 30 c.c. of plain or 0.5 per cent. glucose bouillon. After inoculation with B. tetani, these were cultivated anærobically at 37° C. for three weeks. The result is summarized in the following table.

Culture Media	Growth	Sporulation	Toxicity (Rat) 1 m.l.d.	Hemolytic power (Rabbit corpuscles) 1 m.h.d.
Plain bouillon	good	slight	0.003	0.05
Glucose bouillon	good	slight	0.003	0.05
Plain bouillon + Cholesterin	good	much	0.003	negative
Glucose bouillon + Cholesterin	good	much	0.003	negative
Plain bouillon + Cholesterin palmitate	good	much	0.003	0.5
Glucose bouillon + Cholesterin palmitate	good	much	0.003	0.5
Plain bouillon + Cholesterin stearate	good	much	0.003	0.05
Glucose bouillon + Cholesterin stearate	good	much	0.003	0.05
Plain bouillon + Cholesterin oleate	good	slight	0.003	0.04
Glucose bouillon + Cholesterin oleate	good	slight	0.003	0.03
Plain bouillon + Fresh tissue (Rabbit liver)	good	abundant	0.002	negative
Glucose bouillon + Boiled tissue (Rabbit liver)	good	abundant	0.002	1.0

From this table it will be seen that the presence of cholesterin and various esters of cholesterin in fluid media does not interfere with the growth and the production of spasmin of B. tetani. On the other hand, cholesterin, when added in sufficient amount, removes all hemolytic principle which may have developed in the media. Contrary to cholesterin, cholesterin esters have no neutralizing property against tetanolysin, although cholesterin palmitate appears to be slightly antagonistic to this principle. In this series it was also found that the presence of raw tissues in a culture removes the hemolytic principle more completely than does the boiled.

Discussion.

Dr. C. W. FIELD asked Dr. Noguchi whether, since it seemed that with the cholesterin oleate more hemolytic principles developed, he had tested the oleate in the broth as to its hemolytic properties, and also whether he had tried any inorganic substances which would take up oxygen from the fluid. He believed that the animal tissues were oxydized and thus the medium was more strictly anaerobic.

Dr. NOGUCHI replied that cholesterin oleate is slightly hemolytic by itself, and a slightly higher hemolytic titer of the culture containing this preparation might be explained by this fact. No inorganic reducing agent had been tried. The essential point of the present work was a successful separation of tetanolysin and tetanospasmin in a fluid medium by means of cholesterin or animal tissues.

PATHOLOGICAL INVESTIGATIONS.

MARY A. DIXON JONES, M.D.

Dr. Mary A. Dixon Jones discussed the relationship between fibroid growths and metabolic processes.

A CASE OF ANEMIA DUE TO BOTHRIOCEPHALUS LATUS.

H. L. LYNAH, M.D.

Dr. H. L. Lynah exhibited a specimen of tapeworm of the species Bothriocephalus latus. He called attention to the fact that Bothriocephalus anemia is rare in this country, and said that the worm is not found in the stool except in rare instances. The specimens are usually derived from immigrants from the Baltic coast provinces of Finland and Poland. Only a small proportion of the hosts show an anemia, though it has been demonstrated that the Bothriocephalus is capable of producing severe anemia, and that after expulsion of the worm the person suffering from the anemia may regain perfect health. The patient from whom this worm was obtained was a young man, a Swede, twenty-five years of age, who was suffering from a severe case of tonsillar diphtheria. It was evident from his appearance that he had an anemia of the pernicious type. There was a hemic murmur over the heart. The red cell count was 1,300,000, white cells, 13,000; no eosinophiles. There was moderate poikilocytosis. A few red cells showed granular degeneration and there was moderate polychromatophilia. It was thought that the anemia might be a consequence of the diphtheritic process. The absence of eosinophilia

was misleading as in general intestinal parasites incite an eosinophilia, the one exception being the Bothriocephalus, though occasionally eosinophiles are seen in connection with this parasite. A segment of the worm was, however, found in the stool, and the next day the whole parasite was expelled with the exception of the head which was lost. Dr. Lynah suggested that in some cases the absence of eosinophilia might be important as indicating the presence of Bothriocephalus when a specimen of the worm could not be obtained. The increase in the leucocytes in the blood in this case was undoubtedly due to the diphtheritic infection. A short time after expulsion of the worm the red cells increased to 2,250,000, and the hemoglobin ran up twelve points.